In search of chemical signatures representing biological significance to be applied in the risk assessment process

Chihae Yang[1*], Mitchell A. Cheeseman[1], Ann M. Richard[2], James. F. Rathman[3]
[1] US FDA CFSAN OFAS, College Park, MD 20740
[2] US EPA NCCT, Research Triangle Park, NC 27711
[3] The Ohio State University, Columbus, OH43210
* Contact e-mail: chihae.yang@fda.hhs.gov
* Contact phone: 614-433-7098

Developing computational toxicology methods to assist the risk assessment process has recently gained much attention both in regulatory agencies and industries. The FDA Center for Food Safety and Applied Nutrition's Office of Food Additive Safety (CFSAN OFAS) uses (Q)SAR approaches as part of the evaluation process of new food contact materials, food additives, dietary ingredients, impurities and breakdown products. The structural classes along with currently well-accepted threshold of toxicological concern (TTC) values can be further stratified across various toxicity endpoints. These structural classes across the phenotypes, a major component of the knowledge-base, can be transformed to chemical signatures reflecting the molecular level understanding when they are extracted from the biological assays from high throughput screening experiments anchored to *in vivo* animal effects. The challenges of this new paradigm are being tested through the ToxCast™ program. In our new paradigm, the structural classes provide the link between the correlations of in vivo [structure class × toxicity] and in vitro [structural class × bioassays] datasets. In this paper, the method will be extended to extract the chemical signatures for highly correlated pairs of bioassay and in vivo effects. Statistical correlations will be calculated for 309 chemicals across the assays. These correlations will be then associated with chemical structural classes, from which signatures with high biological significance will be built. This work will demonstrate that understanding toxicity through bioassays may be best navigated through the fingerprint domains of the assays, correlation to in vivo studies, and structural classes. This paper will also discuss how these chemical signatures can assist the construction of the knowledge-base at the US FDA CFSAN OFAS. *This abstract does not reflect EPA policy.*